Original Article

Effect of one minimum alveolar concentration sevoflurane with and without fentanyl on hemodynamic response to laryngoscopy and tracheal intubation

Anwar Hoda, Fauzia A Khan

Department of Anesthesia, Aga Khan University, Karachi, Pakistan

Abstract

Background: Drug combinations can be used for optimum obtundation of the hemodynamic response to tracheal intubation. The objective of this trial was to compare the hemodynamic response to laryngoscopy and tracheal intubation after administration of 2 μg/kg fentanyl bolus or a placebo with 2% end tidal sevoflurane at induction of anesthesia.

Materials and Methods: A total of 70 surgical patients of either gender, age 18-45 years were selected for this double blind, randomized, placebo controlled trial, with 35 in each group. All patients received a standardized induction with thiopentone, atracurium, and an end tidal concentration of 1 minimum alveolar concentration (MAC) sevoflurane. Heart rate and noninvasive blood pressure were compared to the baseline post induction and for seven minutes post intubation. Some adverse events were noted.

Results: The maximum heart rate response was significantly less in the sevoflurane fentanyl group (15% vs. 22%). Significant difference between groups was observed in the systolic blood pressure at six minutes post intubation. Hemodynamic adverse events recorded were similar.

Conclusion: Addition of 2 μg fentanyl bolus to 1 MAC sevoflurane anesthesia at induction attenuated the hemodynamic response to a maximum of 15% above baseline values.

Key words: Anesthetics, hemodynamic response, inhalational, intubation, sevoflurane, tracheal

Introduction

The effect of inhalational anesthetics like halothane,[1] enflurane[2] and isoflurane[3] on the hemodynamic response to tracheal intubation has been studied previously. One of the problems encountered in these earlier studies was the difficulty in controlling the concentration of the delivered agent, which resulted in inadequate control of the response. Currently available monitors continuously monitor the concentration of these agents. Sevoflurane is an inhalational agent that offers hemodynamic advantages like greater depression of the baroreceptor function compared to others and has also been used to attenuate this response.[4] Various doses of fentanyl have been used alone with variable effect to attenuate this response.[5-7]

Multimodal therapy rather than a single agent has been recommended to obtund the sympathetic discharge associated with tracheal intubation.[8] The advantage of combining drugs is that side effects of individual agents will be less because of lower doses used. In this study we compared the effects of adding 2 μg/kg fentanyl or a placebo to one minimum alveolar concentration (MAC) end tidal sevoflurane on the hemodynamic response to laryngoscopy and tracheal intubation. Our end point was to see whether the combination attenuated the response to within 20% of the baseline or not.

Materials and Methods

We obtained institutional ethical committee approval and written informed consent from individual patients. Patients of either gender (aged 18 to 45 years and in ASA grade I, II and III, scheduled to undergo surgery requiring general anesthesia with tracheal intubations) were recruited in

Address for correspondence: Dr. Fauzia A Khan,
Department of Anesthesia, Aga Khan University, Stadium Road,
P.O. Box 3500, Karachi-74800, Pakistan.
E-mail: fauzia.khan@aku.edu

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.86599

this double blind randomized trial. We excluded patients with expected difficult intubations, obesity, hypertension or uncontrolled ischemic heart disease, increased intracranial pressure, and those taking drugs which were known to alter MAC of sevoflurane or affect the heart rate. A sample size of 70 patients was calculated to detect a 20% change in heart rate or blood pressure at 5% significance level and 80% power.

Patients were randomly allocated to either of two groups of equal numbers, sevoflurane alone (group S) or sevoflurane and fentanyl combination (group SF). For randomization, sealed opaque envelopes were prepared by using computer generated random number table. Each envelope had one slip having group name written on it. An anesthetist unconnected to the study pulled out one envelope after identifying patient enrollment and asked a blinded recovery room nurse again unconnected with the study to prepare drugs accordingly. This nurse then prepared placebo (normal saline) or fentanyl in identical 5cc syringes labeled as study drugs. These drugs were then administered by the primary anesthetist blinded to study groups. An assigned research medical officer took all measurements. She was trained for this purpose and was also blinded to the study groups.

All patients were premeditated with oral 7.5 mg midazolam one hour before arrival to the operating room. Group S patients received a standardized induction with intravenous (IV) placebo 5 mls, thiopentone 5 mg/kg and atracurium 0.6 mg/kg. Sevoflurane was administrated along with N_2O and oxygen (60:40 ratio) through the face mask till end tidal MAC of one (2%) was observed on the monitor (Datex AS3, Helsinki, Finland) and it was maintained at this concentration during the rest of study period. Group SF received intravenous fentanyl 2 μg/kg (5 ml) followed by thiopentone and atracurium in identical doses and sevoflurane in the same manner. Tracheal intubation was performed by the primary investigator three minutes after start of induction. Macintosh laryngoscope size 3 for females and size 4 for males, and tracheal tube size 7 mm internal diameter for females and size 8 for males was used.

Baseline heart rate (HR), systolic (SAP), diastolic (DAP), mean arterial pressure (MAP), and oxygen saturation was recorded for three minutes after induction and up to seven minutes post intubation. The study period ended ten minutes after induction of anesthesia. Measurements were taken with same monitor and ECG lead II was monitored continuously. Hypertension was defined as SAP more than 25% of preoperative value and was to be treated with intravenous metoprolol 2 mg bolus. Hypotension was defined as SAP less than 25% of preoperative value and was to be treated with either IV bolus of ephedrine 5 mg or phenylephrine 50 mcg, depending on HR. Tachycardia was defined as HR more than 100 beats per minute and was treated with IV metoprolol 2 mg bolus. Bradycardia was defined as heart rate less than 60 beats per minute and treated with IV atropine 0.5 mg bolus.

Highest and lowest SAP and HR, number of hemodynamic events (hypertension, hypotension, bradycardia, tachycardia or any new arrhythmias) and administration of vasoactive drugs were noted. Time intervals were recorded including induction time (start of anesthetic to loss of the eyelash reflex) and intubation time (start of anesthetic to successful intubation). Any adverse events associated with the induction including coughing, breath holding, laryngospasm, restlessness and pain on injection were noted. All the patients who entered the study completed it and there were no dropouts.

All data was entered, double checked and analyzed by version 16 Statistical Package of Social Sciences (SPSS Inc, 1989-2007, Chicago, USA). Mean of quantitative variables like age, weight, induction time, intubation time and percentage change in HR, SAP, DAP and MAP were compared to baseline and were analyzed using student's *t*-test. Benferroni correction was used. Qualitative variables like number of hemodynamic events, requirement of vasoactive drugs and numbers of adverse events were analyzed by Chi square test. *P* value of less than 0.05 was considered significant.

Results

The two groups were comparable with regard to age, weight, gender distribution, base line HR, SAP, DAP, MAP, and duration of laryngoscopy [Table 1]. There was no difference in the induction and intubation times between the two groups.

Table 1: Baseline demographic characteristics of patients receiving sevoflurane alone or sevoflurane fentanyl combination

Variables	Groups		*P* values
	Sevoflurane (S) (*n*=35)	Sevoflurane and fentanyl (SF) group (*n*=35)	
Age (years)	35.0 (2.4)	39.2 (14.2)	0.22
Weight (kg)	65.7 (1.1)	66.8 (1.2)	0.92
Gender (M:F ratio)	21:14	20:15	0.50
Duration of laryngoscopy (seconds)	12.9 (3.5)	11.9 (2.6)	0.15
Baseline heart rate (beats/min)	88.0 (13.4)	82.7 (13.4)	0.145
Baseline systolic blood pressure (mmHg)	124.0 (15.6)	126.8 (21.7)	0.505
Baseline diastolic blood pressure (mmHg)	75.0 (9.1)	76.6 (13.0)	0.420
Baseline mean blood pressure (mmHg)	90.8 (10.7)	92.5 (14.5)	0.438

Values are in mean (SD) or proportion

HR increased significantly after induction of anesthesia in group S. Maximum rise was at one minute after tracheal intubation (22%, CI: −15.1 to −8.09) and it returned to baseline at six minutes post intubation. In group SF, the HR again increased significantly after induction with the maximum increase seen at one minute post intubation (15%, CI: −8.8 to −7.65). The readings returned to baseline values at four minutes post intubation. The value at seven minutes post intubation was significantly less than the baseline in the SF group. On intergroup comparison a significant difference was seen at all time points with values being lower in SF group [Figure 1].

The SAP response showed a significant rise from baseline at one and two minutes following intubation (16%, CI: −13.1 to −2.2) in the S group. SAP decreased significantly below the base line values at four, five, six and seven minutes. The values in the SF group did not show a significant rise (6%, CI: −15.4 to +2.2] but fell significantly below the baseline at one to three minutes post induction and three, four, five, six and seven minutes post intubation. Intergroup comparison was significant at six minutes post intubation with the value being lower in SF group [Figure 2].

The rise in DAP mirrored the changes in SAP for two minutes following intubation in the S group. The maximum rise was 22% (CI: −21.6 to −13.1) at one minute post intubation. DAP fell significantly below the baseline values at five, six and seven minutes post intubation. The values in the SF group showed a significant fall at one minute post induction, a significant rise at one minute post intubation (11%, CI: −15.1 to −2.8) and again a significant fall at four, five, six and seven minutes post intubation. No significant difference was observed between the groups [Figure 3].

The MAP mirrored the changes in DAP in both the groups. The maximum rise was 18% (CI: −21.6 to −12.5) in the S and 8% in the SF group (CI: −15.0 to −2.2). No significant difference was observed between the two groups [Figure 4].

All these events were recorded from induction of anesthesia till ten minutes post induction. The frequencies and detail of these events are given in Table 2. There were four hemodynamic events in group S compared to three in group SF. The two episodes of hypotension in group SF required treatment with ephedrine and phenylepherine. All episodes of hypertension required treatment with metoprolol. The other adverse events were nine in group S and five in group SF. No myocardial ischemia was observed in any patient. The difference between the groups was not significant.

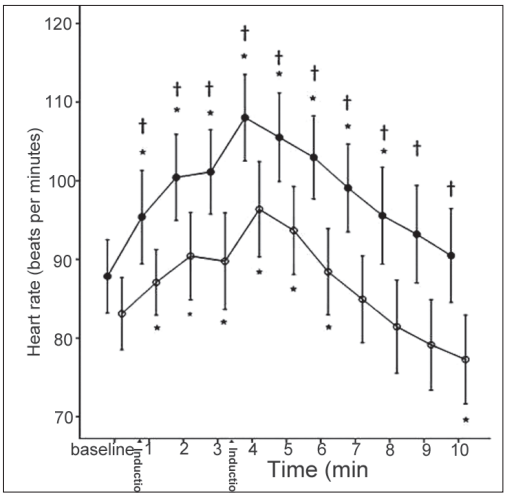

Figure 1: Comparison of heart rate (mean ± SD) between sevoflurane alone (•) and sevoflurane/fentanyl group (○). *indicates significant difference from baseline; †indicates significant difference in heart rate between two groups

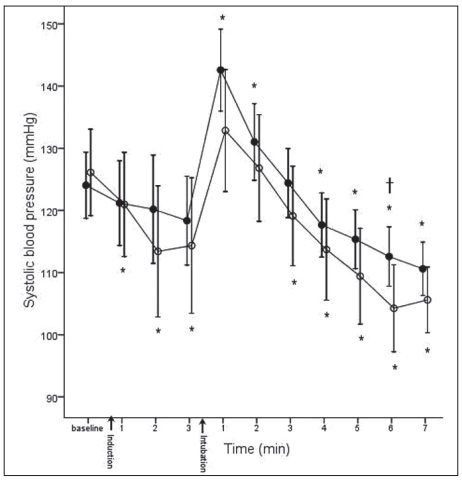

Figure 2: Comparison of systolic blood pressure (mean ± SD) between sevoflurane alone (•) and sevoflurane/fentanyl group (○). *indicates significant difference from baseline; †indicates significant difference in systolic blood pressure between two groups

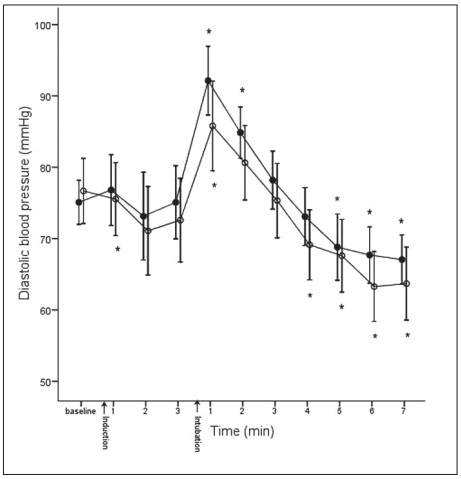

Figure 3: Comparison of diastolic blood pressure (mean ± SD) between sevoflurane alone (•) and sevoflurane/fentanyl group (○). *indicates significant difference from baseline; †indicates significant difference in diastolic blood pressure between two groups

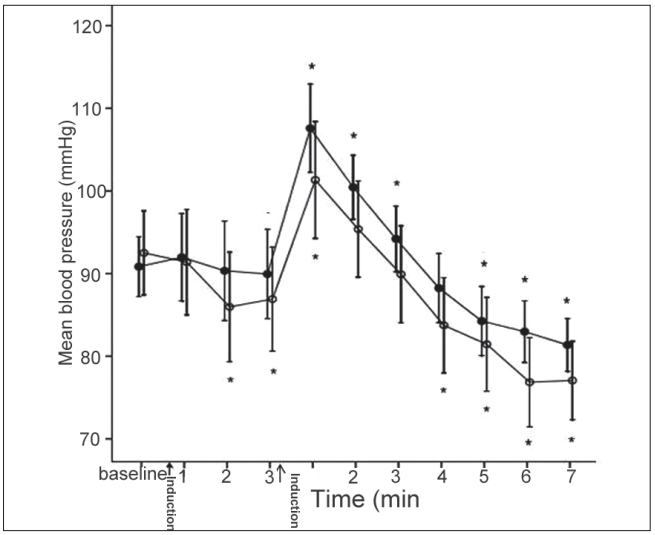

Figure 4: Comparison of mean blood pressure (mean ± SD) between sevoflurane alone (•) and sevoflurane/fentanyl group (○). *indicates significant difference from baseline; †indicates significant difference in mean blood pressure between two groups

Table 2: Comparison of hemodynamic and adverse events during induction between patients receiving sevoflurane alone or sevoflurane fentanyl combination

Adverse events	Sevoflurane alone (*n*=35)	Sevoflurane and fentanyl (*n*=35)	*P* value
Hemodynamic events	4	3	0.2
Hypertension	3	1	
Hypotension	0	2	
Tachycardia	1	0	
Arrhythmia	0	0	
Other adverse events	9	5	0.19
Cough	8	2	
Breath holding and/or laryngospasm at induction	0	3	
Restlessness	1	0	

P value of less than 0.05 was considered as significant

Discussion

Inhalation of volatile anesthetics has been previously used as a technique for suppressing the hemodynamic response to tracheal intubation before. Kautto *et al.* showed that use of 3% enflurane and 2% halothane with nitrous oxide attenuated this rise in blood pressure by 34% and 31% respectively. Cardiac arrhythmias were more common with enflurane.[2]

Availability of literature on the effect of currently used inhalational agents on presser response to laryngoscopy and tracheal intubation is limited. Isoflurane with oxygen and nitrous oxide also attenuates the response but is associated with sympathetic stimulation, and increase in plasma norephinephrine.[3,8] This attenuation is related to the vasodilatory effect of isoflurane. The effect of sevoflurane on the cardiovascular system is different to that of isoflurane. In rabbits, after administration of 1-4% concentration it caused a 50% reduction in MAP without any change in heart rate. This was due to the baroreflex compensation for the effects of sevoflurane on sympathetic and cardiomotor activity up to a concentration of 3%.[9] The same effect has been observed in clinical studies in humans. Autonomic nerve activity was attenuated by sevoflurane administered with N_2O.[10] When 3% isoflurane with 60% N_2O inhalation was compared with 4.5% sevoflurane with 60% N_2O following thiamylal and vecuronium induction in adults, sevoflurane caused a significantly lesser increase in SAP and HR compared to both isoflurane and the control group.[8] It has also been postulated that sevoflurane depresses the sympathetic activity without altering the parasympathetic response.[11] Paisansathan demonstrated that sevoflurane anesthesia decreased cardiac vagal activity and heart rate variability.[12]

Fentanyl has an anti-tussive and an anti-nociceptive effect.[10] In large doses of 6 μg/kg it has been shown to obliterate the pressor response to tracheal intubation completely.[5] In smaller doses the magnitude of attenuation is variable.[6,7] The combined effect of fentanyl during inhalational induction was observed by Katoh *et al.* but without the use of muscle relaxants.[13] Use of fentanyl 1μg/kg^1 decreased the MAC-T1 (50% probability of no movement in response to laryngoscopy and tracheal intubation) from 3.55% to 2% and to 1.45% and 1.37% respectively with the use of 2 and 4 μg/kg.[14] The decrease between 2 and 4 μg/kg dose was not statistically significant.

We were unable to locate any study where the combination of fentanyl with inhalational agent was studied in paralyzed patients. Our rationale was to use this combination to attenuate the response to within 20% of baseline values. We chose fentanyl 2 μg/kg based on Katoh work where this dose reduced MAC-T1 of sevoflurane to 1.45% which is less than one MAC (minimum alveolar concentration).[13] In our study HR response was much less and of a shorter duration in the sevoflurane fentanyl group. The rise in SBP post intubation in the SF group was not significant but this was at the expense of a fall compared to the baseline in the post induction period and three minutes following intubation, which lasted until seven minutes post intubation. This fall was within 15% of baseline values.

Our results showed that one MAC of end tidal sevoflurane alone following induction of anesthesia with thiopentone, and muscle relaxation but without narcotic lead to a rise in HR and the SAP of 22 and 16% respectively compared to the baseline following laryngoscopy and intubation at one minute. Nakayama *et al.* have shown that end tidal anesthetic concentration of two MAC sevoflurane did not prevent hemodynamic response to tracheal intubation, but

they performed tracheal intubation without any muscle relaxation.[14] Tomiyasu[8] also showed an increase in SAP and HR after tracheal intubation with 4.5% sevoflurane and nitrous oxide following thymyl and vecuronium induction. Our results using thiopentone and atracuim induction with sevoflurane 2% alone are similar to their results. Addition of fentanyl 2 μg/kg with the above induction regimen resulted in significant attenuation of HR response and all parameters remained within 15% of baseline values.

One of the critiques on our studies could be the age distribution of our patients between 18 to 45 years which might have affected our results because of the influence of age on MAC of inhalational agents.[15] The second is that we did not use a nerve stimulator to assess neuromuscular relaxation before tracheal intubation.

In conclusion, we would recommend the use of 2 μg/kg fentanyl with 2% end tidal sevoflurane (1 MAC) at induction to maintain the hemodynamic values within 15% of baseline following tracheal intubation. Not many studies have examined the combined effect of fentanyl and a combination of low dose inhalational agents which are used in routine anesthetic practice. We recommend further studies to assess different concentrations of sevoflurane in combination with different doses of fentanyl for obtaining an optimum attenuation of the hemodynamic response to tracheal intubation.

References

1. Turner DA, Shribman AJ, Smith G, Achola KJ. Effect of halothane on cardiovascular and plasma catecholamine responses to tracheal intubation. Br J Anaesth 1986;58:1365-70.
2. Kautto U, Saarnivaara L. Attenuation of the cardiovascular intubation response with N_2O, halothane or enflurane. Acta Anaesthesiol Scand 1983;27:289-93.
3. Bedford R, Marshall W. Cardiovascular response to endotracheal intubation during four anesthetic techniques. Acta Anaesthesiol Scand 1984;28:563-6.
4. Shiro T, Tetsuya H, Hiroaki M, Osamu S, Koji S. Hemodynamic and Catecholamine Responses to Tracheal Intubation during Inhalation of Isoflurane or Sevoflurane. Acta Med Nagasaki 1996;4:76-9.
5. Kautto U. Attenuation of the circulatory response to laryngoscopy and intubation by fentanyl. Acta Anaesthesiol Scand 1982;26:217-21.
6. Helfman S, Gold M, DeLisser E, Herrington C. Which drug prevents tachycardia and hypertension associated with tracheal intubation: Lidocaine, fentanyl, or esmolol? Anesth Analg 1991;72:482-6.
7. Chung K, Sinatra R, Halevy J, Paige D, Silverman D. A comparison of fentanyl esmolol and their combination for blunting the haemodynamic responses during rapid sequence induction. Can J Anaesth 1992;39:774-9.
8. Tomiyasu S, Hara T, Morroka H, Shibata O, Sumikawa K. Haemodynamic and catechol amine responses to tracheal intubation during inhalation of isoflurane or sevoflurane. Acta Med Nagasaki 1996;41:76-9.
9. Ma D, Sapsed-Byrne SM, Chakrabarti MK, Whitwam JG. Effect of sevoflurane on spontaneous sympathetic activity and baroreflexes in rabbits. Br J Anaesth 1998;80:68-72.
10. Nakatsuka I, Ochiai R, Takeda J. Changes in heart rate variability in sevoflurane and nitrous oxide anesthesia: Effects of respiration and depth of Anesthesia. J Clin Anesth 2002;14:196-200.
11. Kurosarva M, Meguro K, Nagayama T, Satio A. Effects of sevoflurane on autonomic nerve activities controlling cardiovascular functions in rats. J Anesth 1989;3:109-17.
12. Paisansathan C, Lee M, Hoffman WE, Wheeler P. Sevoflurane anesthesia decreases cardiac vagal activity and heart rate variability. Clin Auton Res 2007;17:370-4.
13. Katoh T, Nakajima Y, Moriwaki G, Kobayashi S, Suzuki A, Iwamoto T, *et al*. Sevoflurane requirements for tracheal intubation with and without fentanyl. Br J Anaesth 1999;82:561-5.
14. Nakayama M, Kanaya N, Edanaga M, Namiki A. Hemodynamic and bispectral index response to tracheal intubation during isoflurane or sevoflurane anesthesia. J Anesth 2003;17:223-6.
15. Mapleson WW. Effect of age on MAC in humans: A meta-analysis. Br J Anaesth 1996;76:179-85.

How to cite this article: Hoda A, Khan FA. Effect of one minimum alveolar concentration sevoflurane with and without fentanyl on hemodynamic response to laryngoscopy and tracheal intubation. J Anaesth Clin Pharmacol 2011;27:522-6.

Source of Support: Nil, **Conflict of Interest:** None declared.